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Review/Praca poglądowa

Oral mucositis in patients with leukaemia following high-dose chemotherapy and autologous haematopoietic stem cells transplantation

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ABSTRACT

Historically, oral mucositis (OM) has been identified as a symptom developing in patients undergoing irradiation due to head and neck cancers, those undergoing therapy in preparation for a stem cell transplant, or receiving special therapeutic protocols due to acute myeloid leukaemia. It results from direct toxic injury to the mucosal epithelial cells by the immunosuppressive regimen. In this article we want to describe pathogenesis, diagnostic and actual possibility of treatment of OM. The literature reports several rating scale for OM that have been used for patients undergoing cancer therapy. The most useful of them are Oral Toxicity Scale and Oral Mucositis Assessment Scale. In the prevention and treatment of OM associated with standard chemotherapy various drugs and agents acting locally and systemically are used. Many of them are still remaining in the course of research.

Introduction

Haematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of allogeneic or autologous stem cells collected from bone marrow, peripheral blood or umbilical cord blood in patients whose bone marrow or immune system has been damaged. After administered them into the body, their objective is to re-establish haematopoietic function. In allogeneic transplant, a donor of the same species is the source of cells, and in autologous transplant, haematopoietic cells come from the recipient himself or herself. There are also syngeneic transplants (genetically identical twins). Indications for this therapeutic treatment include primarily haematopoietic malignancies, such as leukaemias, lymphomas, myelomas, myelodysplastic syndromes, advanced lung, ovarian, breast, testicular cancers, as well as benign diseases, such as aplastic

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Table 1 – Conditioning regimens in PBSCT

BEAM	BCNU, etoposide, cytarabine, melphalan
BuMel	Busulfan, melphalan in high doses
BorMel	Botezomib, melphalan in high doses
Melphalan	High doses 140–200 mg/m^2

anaemia. Conditioning treatment is required in a patient prior to the HSCT, which involves administering high-dose chemotherapy, often in combination with radiation therapy. Such therapy leads to myeloablation and destruction not only of cancer cells, but also of recipient's haematopoietic system. Non-myeloablative transplants with reduced-intensity conditioning are also used, which involve the application of lower doses of chemotherapy in combination with strong immunosuppressive treatment. Such therapy can be used in older patients over 65 years of age on account of lower toxicity. Negative effects of toxic conditioning therapy include intensified inflammations of the mucous membrane of the mouth, nasopharynx and intestines, so called mucositis [1, 2]. Some groups of anticancer drugs which are used alone or in combination, as chemotherapy before autologous HSCT are particularly often responsible for mucositis. The most recorded mucotoxic agents are: thymidine synthetase inhibitors, such as methotrexate, topoisomerase II inhibitors (etoposide, irinotecan); pyrmidine analogues (cytarabine); purine analogues (6-mercaptopurine and 6-thioguanine); alkylating agents at high doses (busulfan, melphalan and cyclophosphamide); and intercalating drugs (idarubicin, doxorubicin, daunorubicin). When these agents are administered in multiple cycles the risk of mucositis increases at each course [3] (Tables 1 and 2).

Pathomechanism and clinical symptoms of mucositis

Inflammation of the mucous membrane lining the oral cavity and other parts of the gastrointestinal tract and nasopharynx is a serious complication of the above mentioned conditioning therapy, and affects 80–100% of patients [4]. The course is often so severe that patients require strong analgesics and parenteral nutrition [5]. In view of patients' subjective opinions, it is also one of the most intolerable

Table 2 – Groups of anticancer drugs responsible for mucositis

Thymidine synthetase inhibitors	Methotrexate
Topoisomerase II inhibitors	Etoposide
Pyrmidine analogues	Cytarabine
Purine analogues	6-Mercaptopurine, 6-thioguanine
Intercalating drugs	Idarubicin, doxorubicin, daunorubicin

side effects of the therapy. It is a pathological process common for cancer patients receiving radiation therapy, chemotherapy or both of these treatments, and patients requiring autogenic stem cell transplantation. Mucosal injuries affect the entire gastrointestinal tract, from oral cavity to anus [6]. Resulting lesions occurring in epithelium and tunica submucosa are characterised in five clinical phases: (a) initiation, (b) primary damage response, (c) signal amplification, (d) ulceration, and (e) healing [7–10] (Table 3).

Primary mucosal cell injuries resulting from oxidative stress lead to the expression of early response genes and activation of DNA transcription factor. The pathophysiology of mucositis involves various factors, such as nuclear factor kappa B (NF-kappa B) protein complex playing an essential role in the immune response to an infectious agent, cyclooxygenase-2 (COX-2) activated by agents related to the inflammation, pro-inflammatory cytokines – in particular interleukin (IL)-1b (IL)-6, and tumour necrosis factor (TNF) [7, 8]. Clinically, it begins with non-specific oral discomfort preceded by redness, burning sensation, increased sensitivity to sour and hot foods, then erosion and ulcers occur that make it difficult to take and swallow foods, accompanied by a series of other symptoms that make patient's functioning difficult, of which the following should be listed: pain, swelling, fever, mycosis, bacteraemia and sepsis [4, 6, 11, 12]. Then, viral infection symptoms dominate with increased mucosal temperature on hard palate, gingive and dorsum of tongue combined with necrosis and extensive lichenoid lesions. Quantitative and qualitative salivary changes leading to a decrease in salivary IgG, IgA, IgM levels and to xerostomia add to it [6, 9, 12, 13]. As a consequence of the above lesions, microbes appear in the oral cavity which are not present in normal flora in this area, e.g.

Table 3 – The pathobiology of mucositis-five phases

Phase I	Phase II	Phase III	Phase IV	Phase V
Initiation	Primary damage response	Signal amplification	Ulceration	Healing
DNA and non DNA damage	Activation of transcription factors such as NF-kappa B	Positive feedback loops increase cytokine production	Bacteria colonise ulcer surface	Migration and proliferation of regenerative epithelial cells
Reactive oxygen species damage basal epithelial cells	Increased production of TNF-α, IL-1, IL-2, IL-6	Clinically minimal signs and symptoms	Increase the activity of macrophages and production of additional proinflammatory cytokines	Mucosa appears clinically normal
Clinically observed tissue destruction	Activation of sphingomyelinase and ceramide Apoptosis of basal epithelial cells and mucosal damage		Clinically evident erosions	

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